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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/575,199	05/18/2000	Rodney Alan Jue	SCIOS.010CP1	9828
20995	7590	10/27/2003	EXAMINER	
KNOBBE MARTENS OLSON & BEAR LLP			SPECTOR, LORRAINE	
2040 MAIN STREET			ART UNIT	
FOURTEENTH FLOOR			PAPER NUMBER	
IRVINE, CA 92614			1647	

DATE MAILED: 10/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/575,199

Applicant(s)

JUE ET AL.

Examiner

Lorraine Spector, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,5-11,13-21 and 25 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,5-11,13-21 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/03 has been entered.

Claims 1-3, 5-11, 13-21 and 25 are pending and under consideration.

All rejections previously of record have been overcome by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-11, 13-21 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite because they refer to SEQ ID NO: 1 for the sequence of a protein, whereas SEQ ID NO: 1 is a nucleic acid sequence. Mere amendment of the claims to recite SEQ ID NO: 2 is *not* suggested, as SEQ ID NO: 2 is the full-length VEGF₁₂₁, and the numbering of such would not indicate the amino acids that applicants desire. It is suggested that applicants file a *new sequence listing*, and either change SEQ ID NO: 2 to delete the leader sequence and thus have numbering corresponding to mature VEGF₁₂₁, or alternatively introduce a SEQ ID NO: 3 having the mature form and amend the claims and specification accordingly.

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Rejections Over Prior Art

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5-11, 13-21 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tischer et al., U.S. Patent Number 5,194,596, cited by applicants, in view of Claffey et al., BBA 1246:1-9 (1995) U.S. Patent Number 5,648,233(Yamaguchi et al.), and U.S. Patent Number 5,783,416 (Thim et al.).

Tischer et al. disclose recombinant production of VEGF-121; see claims. At column 5, lines 4-16, Tischer et al. state that the VEGF of their invention includes analogs with amino acid substitutions "which retain qualitatively the biological activities of the protein described", that glycosylation is not necessary for protein activity, and that non-glycosylated forms of the protein are envisioned. At column 7 lines 39-41, the glycosylation site is identified as being at Asn74 of their Figure 3a, which is at the sequence position "corresponding" to position 75 of this application (with the caveat that, as stated in the rejection under 35 U.S.C. § 112, second paragraph above, the claims are indefinite in this recitation). At columns 34-35 they specifically

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disclose recombinant production in mammalian cells or bacterial expression systems, and outline at the top of col. 35 a method for refolding protein produced in bacterial cells in a solution comprising glutathione. Pharmaceutical compositions are disclosed at columns 10-12. Although Tischer et al. are silent with respect to whether or not the cysteine residues at position 116 were bound to extraneous cysteine residues, given the examples in the instant specification, in which such occurred with no overt action on the part of the inventors, and in the absence of any added cysteine or glutathione, such is considered to have been inherent to the proteins produced by the methods of Tischer et al. Further, since Tischer et al. disclose using glutathione to refold the protein, it would be expected that proteins having glutathione bound to Cys-116 would also be obtained. The Examiner notes that the case law supports the finding of inherency; in *In re:Swinehart and Sfiligoj* (169 USPQ 226), it was found that "Mere recitation of newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art." In this case, one following the teachings of Tischer et al. would necessarily obtain products consistent with the claims with respect to the moiety bound to Cys 116. Tischer et al. do not teach substitution of Asn75 with Glu (Glutamic acid).

Claffey et.al., BBA 1246:1-9 (1995), disclose that substitution of Asn74 of VEGF with another amino acid, Tyrosine, results in a non-glycosylated protein that is capable of dimerization (page 5) and retains activity indistinguishable from that of the wild-type protein at equimolar concentrations (page 7, second column, page 8 second column). Claffey et al. also report that the Tyr substituted form of the protein was not secreted from mammalian cells as well as the wild-type protein, see page 6.

The person of ordinary skill in the art would immediately recognize that Claffey's substitution of Tyrosine for Asparagine is what is known in the art as a non-conservative substitution, one in which the amino acid being substituted has substantively different chemical properties than the one it replaces, and the conservative substitutions are preferred. For example, U.S. Patent Number 5,648,233 teaches that the most preferred amino acid to be substituted for Asn is Gln, and that Asp, Glu, His, Ser, and Thr are also acceptable, see column 2. U.S. Patent

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Number 5,783,416 (Thim et al.) discloses Asp and Glu as being the preferred substitutions for Asn in eliminating an N-linked glycosylation site, see column 4, lines 48-52.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to alter the protein of Tischer to remove the Asn and thus produce a deglycosylated protein as taught by Claffey et al., in view of Tischer's teaching that non-glycosylated VEGF was a desirable embodiment, and Claffey's demonstration of how to make such. It would further have been obvious to change the Tyr residue used by Claffey et al., which is recognized in the art as being a non-conservative substitution, to another amino acid such as the Glu taught by both U.S. Patent Number 5,648,233 and U.S. Patent Number 5,783,416, which, as evidenced by both patents, is a more preferred substitution for Asn, and less likely to change the properties of the protein. The person of ordinary skill in the art would have been motivated to make this additional change in view of Claffey's teaching that the Tyr form of the protein was not secreted well from cells, and would have expected that the same protein having Glu at that position would be secreted at least as well as the Tyr form and quite possibly better, due to the conservative nature of the substitution as compared to Asn, and additionally would have expected the resultant protein to have wild-type activity, in view of Claffey's teaching that even a non-conservative substitution at that position did not affect the activity of the protein. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

Art of Record

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Patent Number 6,475,796 B1, to Pollitt et al., discloses and claims variants of VEGF with an Arg ->Gln substitution at residue 75 (N75Q). However, the claims therein also specifically require the elimination of Cys 116. At columns 29-30, it is disclosed that the double-mutant N75Q, C116S had unexpectedly high activity as compared to the single N75Q mutant. There is no comparison of the mutein currently claimed herein to wild-type VEGF.

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Advisory Information


Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.


 Lorraine Spector, Ph.D.
 Primary Examiner